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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/066,359	01/31/2002	Scot R. Weinberger	CiphBio-9	5296

1473 7590 07/23/2003

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EXAMINER	
DAVIS, DEBORAH A	
ART UNIT	**PAPER NUMBER**
1641	11

DATE MAILED: 07/23/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/066,359	WEINBERGER ET AL.	
	Examiner	Art Unit	
	Deborah A Davis	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 June 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-26* is/are pending in the application.

4a) Of the above claim(s) *1-5 and 15-26* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *7-14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Election/Restrictions

1. Applicant's election without traverse of Group II in Paper No. 10 is acknowledged.

Specification

2. The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 6-14 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

5. Claim 6 recites the limitation "differentially displayed" in the preamble and in steps (a) through (d) is vague because it is unclear as to what this term means. There is no definition in the specification that explains to one skilled in the art as to what this limitation means. Please clarify.

6. Claim 7 recites the limitation "differentially expressed" in lines 9, 19, 21 is vague for the same reasons disclosed in claim 6.

7. Claim 7 recites the limitation "differentially expressed" in line 38 is vague for the same reasons disclosed in claim 6.

8. Claim 7, recite the limitation "the protein biochip" in line 4 of step (c) lack antecedent basis.

9. Claim 9, recites the limitation "differentially displayed" in line 9 is vague for the same reasons disclosed in claim 6.

Claim Rejections - 35 USC § 103

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

11. Claims 6 and 8-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over William T. Hutchens (WO98/59362) in view of Dongre et al (Emerging tandem-mass-spectrometry techniques for the rapid identification of proteins, TIBTECH, Vol. 15, October 1997).

The instant claims are directed to a method for identifying a protein that is differentially displayed between two complex biologic samples using mass spectrometry. William T. Hutchens teaches methods for identifying analytes that are differentially expressed between biological materials using desorption spectrometry (see abstract). The two samples are differentially displayed because the proteins can be expressed in different cell types being normal versus pathologic cancer cells. The

method may indicate that a protein or other biomolecule is increased or decreased in expression, or is changed in some way based on different mass (page 63, lines 1-32). Claim 6, steps (b) through (c) is directed to fragmenting proteins in two samples and detecting protein fragments determining the identity and correlating the fragments that are differentially displayed between the two samples. William T. Hutchens teaches that the fragmenting of large proteins into smaller pieces by enzymatic digestion increases sensitivity in detection of protein fragments. Fragmentation can be achieved by any means known in the art; some examples are enzymes such as glycosidase, endoproteases (page 64, lines 28-32). William T. Hutchens teaches proteins that are differentially present in two samples will increase the number of signals from that protein (page 64, lines 11-24). William T. Hutchens teaches that these methods of protein identification are useful for identifying diagnostic markers of disease expressed in a patient sample or a diseased cultured cell compared to normal samples (page 64, lines 1-10). Maps of the protein samples are compared, which may indicate increased or decreased expression in a protein (page 63, lines 22-32). Accordingly, the matched parameters can be set to identify the closeness-of-fit between the protein analyte characteristics and the characteristics of the reference polypeptides in the database (page 61, lines 15-31). William T. Hutchens' method further includes a capture probe to capture proteins. William T. Hutchens' instant reference teaches probes for the specific detection of one or more analytes by desorption spectrometry, which can be prepared by selecting markers to be detected (page 59, lines 19-33).

The instant reference of William T. Hutchens does not teach utilizing the method with tandem mass spectrometry; neither does it teach steps of a secondary fragmentation step to generate parent peptides with a gas phase.

However, Dongre et al provides an overview of techniques and methodologies for identification of proteins and peptides from complex biological samples utilizing tandem mass spectrometry (see abstract). Tandem mass spectrometry is commonly used for sequence analysis of peptides and proteins that include techniques such as Collision Induced Dissociation (CID) that involves the collision of peptide ions in a gas phase at low speeds with an inert gas such as argon. The fragment ions generated from the gas collision, upon peptide-ion activation are then analyzed by a second mass analyzer (page 419, column 1 and Figure 1). The correct amino acid sequence is frequently identified purely on the basis of the preliminary score and a closeness-to-fit method is used to confirm the highest-scoring amino acid sequence and increase the sensitivity of the search (page 423, column 1, paragraph 1).

It would have been obvious to one of ordinary skill in the art to modify the reference of William T Hutchens to include tandem mass spectrometry and a secondary fragmenting step for generating peptides using gas as taught by Dongre et al because tandem mass spectrometry has several advantages. First, identification is possible on the basis of a single peptide spectrum. Second, each tandem mass spectrum represents an independent piece of information, and so additional spectra that match the same protein add considerable strength to the identification. Third, the ability to identify proteins based on a single tandem mass spectrum allows the identification of

proteins present in complex mixtures. Finally, post-translational modification do not appear to complicate the identification and can be placed within the amino acid sequence at the specific site of modification with the aid of computer programs (page 424, column 2, paragraph 2). Utilizing a secondary fragmenting step for generating peptides is also a method utilized by tandem mass analyses. This step is an advantage for tandem mass spectrometry because under low and high-energy gas-phase collision induced dissociation (CID) conditions, peptide ions that are generated mostly fragment at the peptide bonds along the backbone, generating a ladder of sequence ions. This information dictates which type of amino acid sequence will form and have lead to sequencing methods which is important when predicting peptide-fragmentation patterns (page 419, column 1).

12. Claims 6, and 8-14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Liebler et al (USP# 6,379,970) in view of Dongre et al (Emerging tandem-mass-spectrometry techniques for the rapid identification of proteins, TIBTECH, Vol. 15, October 1997).

The instant claims are directed to a method for identifying a protein that is differentially displayed between two complex biologic samples using mass spectrometry.

Liebler et al teaches a method for detecting peptide fragments of protein(s) that are differentially present in biological samples. The identity of the peptides may be determined and correlated with the protein(s) that are differentially present in the

samples (see abstract). Claim 6, steps (b) through (c) is directed to fragmenting proteins in two samples and detecting protein fragments determining the identity and correlating the fragments that are differentially displayed between the two samples. Liebler et al teaches protein fragmentation wherein the proteins are digested in a plurality of biological samples to produce peptides in each sample; separating the peptides in the samples and identifying the peptides that are differentially present. The proteins contained in the biological samples may be digested with any of the well-known protein digestions reagents. Such reagents may be chemical or enzymatic (col. 5, lines 15-26 and col. 10, lines 1-20). The instant claim 6 utilizes mass spectrometry for detection of peptide and proteins. Liebler et al teaches that a variety of mass spectrometry techniques are routinely used to determine peptide sequence. Two MS ionization methods used in the field of protein analysis are electrospray ionization (ESI) and matrix assisted laser desorption ionization (MALDI). Both methods are effective means of producing gas phase ions of proteins peptides and other biomolecules for MS analysis (col. 7 lines 30-65). One non-limiting embodiment of the present invention involves the analysis of two peptide mixtures together in one analytical run. Once the mixtures are combined and then subjected to some analytical separation the differential expression of the precursor protein are then selected for further analysis by mass spectrometry (col. 4, lines 32-45). Correlation of differentially produced peptides with differentially expressed proteins is performed by using amino acid sequences of signature peptides against a database of protein sequences (col. 8, lines 38-67).

Samples may comprise of cultured cells, blood samples, biopsy or other biological fluids.

Liebler et al does not particularly point out using tandem mass spectrometry as recited in claim 6.

However, Dongre et al provides an overview of techniques and methodologies for identification of proteins and peptides from complex biological samples utilizing tandem mass spectrometry (see abstract). Tandem mass spectrometry is commonly used for sequence analysis of peptides and proteins that include techniques such as Collision Induced Dissociation (CID) that involves the collision of peptide ions in a gas phase at low speeds with an inert gas such as argon. The fragment ions generated from the gas collision, upon peptide-ion activation are then analyzed by a second mass analyzer (page 419, column 1 and Figure 1). The correct amino acid sequence is frequently identified purely on the basis of the preliminary score and a closeness-to-fit method is used to confirm the highest-scoring amino acid sequence and increase the sensitivity of the search (page 423, column 1, paragraph 1).

It would have been obvious to one of ordinary skill in the art to modify the reference of Liebler et al to include tandem mass spectrometry and a secondary fragmenting step for generating peptides using gas as taught by Dongre et al because tandem mass spectrometry has several advantages. First, identification is possible on the basis of a single peptide spectrum. Second, each tandem mass spectrum represents an independent piece of information, and so additional spectra that match the same protein add considerable strength to the identification. Third, the ability to

identify proteins based on a single tandem mass spectrum allows the identification of proteins present in complex mixtures. Finally, post-translational modification do not appear to complicate the identification and can be placed within the amino acid sequence at the specific site of modification with the aid of computer programs (page 424, column 2, paragraph 2). Utilizing a secondary fragmenting step for generating peptides is also a method utilized by tandem mass analyses. This step is an advantage for tandem mass spectrometry because under low and high-energy gas-phase collision induced dissociation (CID) conditions, peptide ions that are generated mostly fragment at the peptide bonds along the backbone, generating a ladder of sequence ions. This information dictates which type of amino acid sequence will form and have lead to sequencing methods which is important when predicting peptide-fragmentation patterns (page 419, column 1).

13. Claim 7 is rejected under 35 U.S.C. 103(a) as being unpatentable over William T. Hutchens in view of Dongre et al and further in view of Little et al (USP#6,322,970).

The teachings of William T. Hutchens in view of Dongre et al are set forth above and differ from the instant claim in not specifically pointing out analyzing capture proteins on a probe.

However, Little et al teaches methods of detecting polypeptides using mass spectrometry. Little et al teaches using a microchip to isolate a polypeptide as well as a means to manipulate the isolated target polypeptide prior to mass spectrometry. In particular embodiments, post-translational capture and immobilization of a target polypeptide are provided in order to sequence a polypeptide. This method includes

immobilizing the target polypeptide to a solid surface and cleaving the fragments with enzymatic treatment, which will improve mass spectrometric analysis (col. 4, lines 24-67 and col. 6, lines 10-15).

It would have been obvious to one of ordinary skill in the art to modify the teachings of William T. Hutchens in view of Dongre et al to include a microchip as taught by Little et al to capture proteins fragments because it will improve mass spectrometric analysis of protein fragments.

Conclusion

14. No claims are allowed.

15. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure:

A. Asada et al teaches a method and system for computer-aided differential diagnosis of diseases using neural networks (USP#5,463,548).

B. Yates et al teaches a method for correlating a peptide fragment mass spectrum with amino acid sequences derived from a database using tandem mass (USP#5,538,897).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Deborah A Davis whose telephone number is (703) 308-4427. The examiner can normally be reached on 8-5 Monday thru Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le can be reached on (703) 305-3399. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1123.

Deborah A. Davis
CM1, 7D16
July 14, 2003

LONG V. LE
SUPERVISORY PATENT EXAMINER
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07/14/03